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INTELLECTUAL PROPERTY **INDIA**

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Provisional Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.* ***1304/Del/2003*** *dated* ***22nd October 2003.***

Witness my hand this 17th day of January 2005.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

FORM 1

THE PATENTS ACT, 1970

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"PROCESS FOR THE PREPARATION OF HMG-CoA REDUCTASE INHIBITORS"**

(b) that the Provisional Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. YATENDRA KUMAR
b. MOHAMMAD RAFEEQ
c. SHANTANU DE
d. SWARGAM SATHYANARAYANA

1304 DEL 03
22 OCT 2003

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.
Tel. No. (91-124) 2343126, 2342001–10; 5012501-10

9. Following declaration was given by the inventors or applicants in the convention country:

We, YATENDRA KUMAR, MOHAMMAD RAFEEQ, SHANTANU DE, SWARGA SATHYANARAYANA of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vih Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first invento for this invention or applicant in the convention country declare that the applicant herein, **Ranba Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is o assignee or legal representatives.

a. (YATENDRA KUMAR)

b. (MOHAMMAD RAFEEQ)

c. (SHANTANU DE)

d. (SWARGAM SATHYANARAYANA)

10. That to the best of our knowledge, information and belief the fact and matters stated herein ar correct and that there is no lawful ground of objection to the grant of patent to us on thi application.

11. Followings are the attachment with the application:
    a. Provisional Specification (3 copies)
    b. Drawings (3 copies)
    c. Priority document(s)
    d. Statement and Undertaking on FORM – 3
    e. Power of Authority (Not required)
    f. Fee Rs.3,000/- (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on

We request that a patent may be granted to us for the said invention.

Dated this **17TH** day of **October, 2003.**

For Ranbaxy Laboratories Limite

(SUSHIL KUMAR PATAWA
Company Secret

FORM 2

The Patents Act, 1970

(39 of 1970)

PROVISIONAL SPECIFICATION

(See Section 10)

1704 DEL 03

PROCESS FOR THE PREPARATION OF HMG-COA REDUCTASE INHIBITORS

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

This invention relates to a process for the preparation of HMG CoA reductase inhibito and in particular rosuvastatin calcium.

The invention describes the process for preparation of amorphous rosuvastatin calcium from crystalline rosuvastatin calcium, rosuvastatin methyl ammonium salt and from rosuvastatin lactone.

Rosuvastatin calcium is chemically, (3R,5S,6E)-7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]-3,5-dihydroxy-6-heptenoic acid, calcium salt (2:1) of formula I, as shown in the accompanied drawings. It is an antihypercholesterolemic drug used in the treatment of atherosclerosis.

Hypercholesterolemia is now well recognized as a primary risk in coronary heart disease. Clinical studies with lipid lowering agents have established that decreasing elevated serum cholesterol level reduces the incidence of cardiovascular mortality. Pravastatin (Pravachol) and simvastatin (Zocor), which are fungal metabolites or of the chemical modifications are known as the first generation of drugs for the treatment of atherosclerosis by inhibiting the activity of HMG-CoA reductase. Recently, synthetic inhibitor of HMG-CoA reductase such as fluvastatin (Lescol) is developed as the second-generation drugs. Cerivastatin (Baycol) along with atorvastatin (Lipitor), are third-generation inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG- CoA) reductase, a key enzyme in cholesterol synthesis.

To obtain more potent reductase inhibitors, efforts were made to replace the complex decalin portion of the mevinic acids (lovastatin and pravastatin) with structurally simpler and achiral aromatic surrogates.

It has recently been found that the so-called "superstatin", rosuvastatin calcium has consistently shown greater potency than other marketed statins (atorvastatin, simvastatin and pravastatin) in preclinical and clinical testing.

Preparation of rosuvastatin hemicalcium salt is described by Shionogi in US Patent No. RE 37314.

The difference in the activity of different polymorphic forms of a given drug has drawn the attention of many workers in recent years to undertake the studies on polymorphism. This has especially become very interesting after observing that many antibiotics, antibacterials, tranquilizers etc. exhibit polymorphism and some/one of the polymorphic forms of a given drug exhibit superior bioavailability and consequently show much higher activity compared to other polymorphs. The term polymorphism includes different physical forms, crystal forms, and crystalline / liquid crystalline / non-crystalline (amorphous) forms.

It has also been disclosed that the amorphous forms in a number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to the crystalline form [Konne T., Chem. Pharm. Bull. 38, 2003 (1990)]. For some therapeutic indications one bioavailability pattern may be favoured over another. Cefuroxime axetil is the classical example of amorphous form exhibiting higher bioavailability than the crystalline form.

US Patent No. RE 37314 describes a process for preparation of amorphous rosuvastatin calcium by dissolving the corresponding sodium salt in water, adding calcium chloride and collecting the resultant precipitate by filtration.

US Patent No. 6,589,959 describes a process for preparation of crystalline form A of rosuvastatin by warming the amorphous form of rosuvastatin calcium in a mixture of water and acetonitrile; cooling the resultant solution to ambient temperature and then filtering the product which is then dried at 50°C under vacuum to give crystalline Form A of rosuvastatin calcium.

It is our reasoned belief that amorphous rosuvastatin would be more effective pharmaceutically over the crystalline form. The US Patent No. 6,589,959 states that the material obtained by the process described in RE 37314 patent provides amorphous material. The present inventors have determined that the material so obtained is difficult to isolate and handle thus making it unsuitable for commercial level use. The purity of the said amorphous rosuvastatin calcium is about 96 to 98% with an impurity content of about 2 to 4%. The prominent impurity is the unwanted diastereomeric impurity which is more than 1%.

Surprisingly, the inventors of the present invention have found that amorphous rosuvastatin calcium when made by the process of the present invention is easy to isolate and handle thus making the process amenable for commercial scale use. The purity of the amorphous rosuvastatin calcium of the present invention is greater than 99% with diastereomeric impurity less than 0.5%.

A first aspect of the invention provides amorphous rosuvastatin calcium of Formula I, as shown in the accompanied drawing from the crystalline rosuvastatin calcium. Amorphous rosuvastatin calcium substantially free of crystalline rosuvastatin calcium is also included within the scope of the invention. The purity of the amorphous form is greater than 99% with diastereomeric impurity less than 0.5%. More preferably the purity is greater than 99.5% with diastereomeric impurity less than 0.25% and most preferably the purity is greater than 99.8% with diastereomeric impurity less than 0.15%.

A second aspect of invention provides a process for preparing amorphous rosuvastatin calcium from crystalline form which comprises of

a) dissolving the crystalline form in a suitable organic solvent.
b) removing the solvent from the said solution
c) recovering the amorphous rosuvastatin calcium.

Crystalline rosuvastatin calcium is prepared by methods described in the US Patent No. 6,589,959. The said crystalline form is dissolved in an organic solvent. The solvent is then removed from said solution to get rosuvastatin calcium in amorphous form. The amorphous rosuvastatin calcium thus obtained can be dried using conventional drying techniques such as vacuum tray drying, rotary vacuum drying, fluidized bed drier, tray drying and the like.

The organic solvent can be selected from a group comprising of lower alkanols, ethers, esters, ketones, polar aprotic solvents or mixtures thereof. The lower alkanol is selected from methanol, ethanol, isopropanol and n-propanol. The ethers are selected from tetrahydrofuran and 1,4-dioxane. The esters are selected from ethyl formate, methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate, butyl acetate and amyl acetate. The ketones are selected from acetone, ethyl methyl ketone, methyl isobutyl ketone and diisobutyl ketone. Polar aprotic solvents are selected from

N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone.

The solution of crystalline rosuvastatin calcium is prepared in the organic solvent by optional warming to dissolve the solids completely. If required the solution can be clarified to remove the undissolved foreign particulate matter. The said solution is then concentrated to remove solvent. The concentration can be carried out under vacuum of about 100 to 0.01 mm of Hg wherein the solvent is removed by vacuum distillation of the solution while optionally heating the solution at a temperature of about 15 to 55°C to effect faster removal of the solvent.

The solvent can also be removed by spray-drying the solution of crystalline rosuvastatin calcium using a spray-dryer. For the purpose of spray-drying, mini-spray Dryer (Model : Buchi 190 Switzerland) which operates on the principle of nozzle spraying in an parallel - flow i.e. the sprayed product and the drying gas flow in the same direction was used. The drying gas can be air or inert gases such as nitrogen, argon or carbon dioxide. Nitrogen is preferred in this case.

A third aspect of the present invention provides a process for preparing amorphous rosuvastatin calcium from crystalline form which comprises of

a) dissolving the crystalline form of rosuvastatin calcium in a suitable first organic solvent
b) adding a second organic solvent to the solution or solution to second organic solvent in optional order of succession in which rosuvastatin calcium is insoluble or very slightly soluble or sparingly soluble, such that amorphous rosuvastatin precipitates out from the solution
c) isolating the amorphous rosuvastatin calcium from the mixture.

Crystalline rosuvastatin calcium is dissolved in a first organic solvent and to the solution added a second solvent or solution to the second organic solvent in optional order of succession in which rosuvastatin is insoluble or very slightly soluble or sparingly soluble. Due to addition of the second solvent, rosuvastatin calcium precipitates out from the solution. The precipitated product is then isolated and dried by conventional techniques to get the amorphous rosuvastatin calcium.

The suitable first organic solvent can be selected from a group comprising of lower alkanols, ethers, esters, ketones, polar aprotic solvents or mixtures thereof. The lower alkanol is selected from methanol, ethanol, isopropanol and n-propanol. The ethers are selected from tetrahydrofuran and 1,4-dioxane. The esters are selected from ethyl formate, methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate, butyl acetate and amyl acetate. The ketones are selected from acetone, ethyl methyl ketone, methyl isobutyl ketone and diisobutyl ketone. Polar aprotic solvents are selected from N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone.

The second organic solvent which characterized by the fact that rosuvastatin is insoluble (10,000 and over parts of solvent required for 1 part of solute as per United States Pharmacopoeia 2002) or very slightly soluble (form 1,000 to 10,000 parts of solvent required for 1 part of solute as per United States Pharmacopoeia 2002) or sparingly soluble (from 30 to 100 parts of solvent required for 1 part of solute as per United States Pharmacopoeia 2002) can be selected from a group of solvents comprising of isopropanol, isobutanol, n-butanol, cyclopentane, cyclohexane, cycloheptane, hexane, petroleum ether, heptane, diethyl ether, diisopropyl ether or mixtures thereof.

The term, "insoluble", "very slightly soluble" or "sparingly soluble" mentioned, herein onwards has the same meaning as defined above and is in accordance with the description provided in the United States Pharmacopoeia 2002.

A fourth aspect of the invention provides a process for preparing amorphous rosuvastatin calcium from crystalline form which comprises of

a) subjecting the crystalline rosuvastatin calcium to milling until the said crystalline form is converted to amorphous form
b) optionally drying the amorphous form.

Crystalline rosuvastatin calcium solid or its slurry in an organic solvent is milled by grinding action between two surfaces. Such milling is carried out by using a traditional technique of compounding using a pestle and mortar or by milling machines that essentially work the same principle. Examples of such milling machines include various

makes of ball mills, roller mills, gyratory mills, and the like. The slurry of crystalline rosuvastatin calcium in an organic solvent can be of 30 to 85% w/v.

The organic solvent which characterized by the fact that rosuvastatin is insoluble or very slightly soluble or sparingly soluble can be selected from a group of solvents comprising of isopropanol, isobutanol, n-butanol, cyclopentane, cyclohexane, cycloheptane, hexane, petroleum ether, heptane, diethyl ether, diisopropyl ether or mixtures thereof.

A fifth aspect of the present invention provides a process for preparing amorphous rosuvastatin calcium from crystalline form which comprises of

a) dissolving crystalline rosuvastatin calcium in an organic solvent optionally containing water and
b) freeze drying or lyophilizing the said solution to get amorphous rosuvastatin calcium.

A solution of crystalline rosuvastatin calcium in an organic solvent optionally containing water is prepared and treated with charcoal, filtered to remove charcoal. The clear solution is then freeze-dried by conventional techniques to get the amorphous rosuvastatin calcium. The amorphous form can then be dried under vacuum.

The organic solvent can be selected from a group comprising of lower alkanols, ethers, esters, ketones, polar aprotic solvents or mixtures thereof. The lower alkanol is selected from methanol, ethanol, isopropanol and n-propanol. The ethers are selected from tetrahydrofuran and 1,4-dioxane. The esters are selected from ethyl formate, methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate, butyl acetate and amyl acetate. The ketones are selected from acetone, ethyl methyl ketone, methyl isobutyl ketone and diisobutyl ketone. Polar aprotic solvents are selected from N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone.

A sixth aspect of the present invention provides a process for preparation of amorphous rosuvastatin calcium from crystalline rosuvastatin calcium which comprises of

a) dissolving the crystalline rosuvastatin calcium in a suitable organic solvent

b) adding water to the solution of rosuvastatin or solution of rosuvastatin to water in optional order of succession, such that rosuvastatin precipitates out from the solution

c) isolating the amorphous rosuvastatin calcium from the mixture.

Crystalline rosuvastatin calcium is dissolved in an organic solvent and the solution can be optionally treated with charcoal or clarified to remove foreign particulate matter. The clear solution can be obtained by gently warming the mixture as well. To the clear solution water is added at such a rate that rosuvastatin calcium precipitates very slowly. The mixture after complete addition of water can be chilled or partially concentrated to remove the organic solvent. The separated amorphous form is then filtered and dried as per the methods described earlier.

The suitable organic solvent can be selected the group comprises of methanol, ethanol, isopropanol, n-propanol, tetrahydrofuran, 1,4-dioxane, acetone, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone or mixtures thereof.

A seventh aspect of the present invention provides a process for preparation of amorphous rosuvastatin calcium from rosuvastatin methyl ammonium salt of Formula II which comprises of

a) lactonizing the rosuvastatin methyl ammonium salt of Formula II

b) optionally isolating the rosuvastatin lactone of Formula III.

c) converting the rosuvastatin lactone to the amorphous rosuvastatin calcium by treatment with a base and a calcium salt.

d) recovering the amorphous rosuvastatin calcium by filtration.

Rosuvastatin methyl ammonium salt of Formula II as shown in the accompanied drawing is prepared by the process described in PCT application WO 01/60804. It is treated with an acid at a pH of about 1 to 5 to get rosuvastatin lactone of Formula III as shown in the accompanied drawing. The reaction is carried out in presence of first organic solvent optionally containing water at a temperature of about -10 to 100°C. After completion of the reaction, the layers are separated and organic layer after washing with water and/or brine is concentrated completely under vacuum. The residue is taken up in a second organic solvent. The mixture can be stirred at a temperature of

about 40 to 150°C for about 1 to 50 hours to affect lactonization. After completion of lactonization, the second organic solvent can be removed from the reaction mass under vacuum and the residue can be treated with third organic solvent to get the rosuvastatin lactone. The residue can be as such taken in the next step without actually isolating the lactone.

The acid is selected from a group comprising of inorganic mineral acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid or organic acids such as formic acid, acetic acid and the likes.

The first organic solvent is selected from the water immiscible or partially miscible organic solvents selected from a group comprising of toluene, xylene, benzene, ethyl methyl ketone, diisobutyl ketone, methyl isobutyl ketone, methyl t-butyl ether, diisopropyl ether, ethyl acetate, methyl formate, methyl acetate, isobutyl acetate, n-propyl acetate, isopropyl acetate, amyl acetate or mixtures thereof.

Second organic solvent is selected from a group comprising of methyl t-butyl ether, toluene, xylene, benzene, diisopropyl ether, n-butanol, isobutyl acetate, ethyl methyl ketone, diisobutyl ketone or mixtures thereof.

Third organic solvent which characterized by the fact that rosuvastatin is insoluble or very slightly soluble or sparingly soluble can be selected from a group of solvents comprising of isopropanol, isobutanol, n-butanol, cyclopentane, cyclohexane, cycloheptane, hexane, petroleum ether, heptane, diethyl ether, diisopropyl ether or mixtures thereof.

The lactone of Formula III is then dissolved in an organic solvent optionally containing water and treated with a base at a temperature of about 10 to 100°C for about 1 to 40 hours to effect hydrolysis of the lactone. The reaction mass pH during the reaction can be adjusted in the range of about 7.5 to 11 using a base. The solvent is then removed and the residue can be taken up in water. The aqueous solution is washed with first organic solvent as described earlier in this aspect and then treated with calcium ions after which rosuvastatin calcium precipitate from the aqueous solution as amorphous solid. The said amorphous rosuvastatin calcium is then isolated and dried.

The base is selected from a group comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and potassium bicarbonate.

The calcium ions can be generated by using a calcium compound selected from a group comprising of calcium chloride, calcium hydroxide, calcium carbonate, calcium acetate, calcium sulphate, calcium borate, calcium tartarate, calcium bromide or any other compound capable of generating calcium ions.

An eighth aspect of the present invention provides a process for the preparation of amorphous rosuvastatin calcium from rosuvastatin methyl ammonium salt of Formula II which comprises of

a) treating rosuvastatin methyl ammonium salt with a base and a calcium salt
b) isolating the amorphous rosuvastatin calcium from the reaction mass.

The examples of base and calcium salt are described in detail in sixth aspect of the invention.

The conversion can be easily carried out in presence of water optionally containing an organic solvent. The reaction temperature can be kept at about -5 to 100°C.

The organic solvent can be selected from a group comprising of lower alkanols, ethers, esters, ketones, polar aprotic solvents, alkyl or cycloalkyl hydrocarbons or mixtures thereof. The lower alkanol is selected from methanol, ethanol, isopropanol, isobutanol, n-butanol and n-propanol. The ethers are selected from tetrahydrofuran, 1,4-dioxane, diethyl ether and diisopropyl ether. The esters are selected from ethyl formate, methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate, butyl acetate and amyl acetate. The ketones are selected from acetone, ethyl methyl ketone, methyl isobutyl ketone and diisobutyl ketone. Polar aprotic solvents are selected from N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone. Alkyl or cycloalkyl hydrocarbons can be selected from group comprising of cyclopentane, cyclohexane, cycloheptane, hexane, petroleum ether, heptane or mixtures thereof.

A ninth aspect of the present invention provides a process for preparation of amorphous rosuvastatin calcium from rosuvastatin methyl ammonium salt of Formula II which comprises of

a) lactonizing the rosuvastatin methyl ammonium salt of Formula II
b) optionally isolating the rosuvastatin lactone of Formula III.
c) converting the lactone form of rosuvastatin to the amorphous rosuvastatin calcium by treatment with a base and a calcium salt.
d) removing the water from the reaction mass by azeotropic distillation using an organic solvent
e) recovering the amorphous form of rosuvastatin calcium by removing the organic solvent from the resultant solution.

Rosuvastatin methyl ammonium salt is converted to rosuvastatin calcium as described in the sixth aspect of the invention. However, after treating the aqueous layer with calcium ions, to the reaction mass is added a suitable organic solvent capable or azeotropically removing water and simultaneously capable of dissolving rosuvastatin calcium. From the resulting mixture water was removed and from the solution of rosuvastatin calcium, solvent was removed to get the desired amorphous rosuvastatin calcium as solid.

Alternatively after treatment with calcium ions, to the reaction mass is added an organic solvent which dissolves rosuvastatin calcium and is immiscible or partially miscible with water. The solvent can be made immiscible in water by increasing the salinity of the aqueous layer using sodium chloride or calcium chloride. The layers are separated and the organic layer containing rosuvastatin calcium is then dried over calcium chloride, sodium sulphate or molecular sieves to remove traces of water. The organic layer is then concentrated to remove solvent to get the desired amorphous rosuvastatin calcium. The said concentration can be effected by either spray-drying or by vacuum distillation.

The organic solvent can be selected from a group comprising of tetrahydrofuran, 1,4-dioxane, toluene, xylene, dichloromethane, ethyl formate, methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate, butyl acetate, amyl acetate, ethyl methyl ketone, methyl isobutyl ketone and diisobutyl ketone or mixtures thereof.

A tenth aspect of the invention provides a process for converting a mixture of amorphous and crystalline form of rosuvastatin calcium to completely amorphous rosuvastatin calcium.

A mixture of largely amorphous with some crystalline rosuvastatin calcium can be prepared directly from the reaction mixture or from the crystalline form or from the amorphous rosuvastatin calcium by the process already described in the specification with little variations. The crystalline rosuvastatin calcium can be converted to a mixture of amorphous and crystalline material by the technique described in the third aspect of the invention.

The said mixture of largely amorphous rosuvastatin calcium containing some crystalline form is then converted to the amorphous form by the techniques already described in the earlier aspects.

An eleventh aspect of the present invention provides a process of preparation of amorphous rosuvastatin calcium from crystalline rosuvastatin calcium which comprises of

a) treating crystalline rosuvastatin calcium with an acid to obtain rosuvastatin
b) optionally isolating rosuvastatin
c) converting rosuvastatin to amorphous rosuvastatin calcium by treatment with a base and calcium salt.

The examples of base and calcium salt are described in detail in seventh aspect of the invention.

The acid used can be selected from a group comprising of inorganic acid such as hydrochloric acid, sulphuric acid, phosphoric acid, hydrobromic acid, nitric acid and the like or a mixture thereof. The acid can be organic acid selected from group comprising of formic acid, acetic acid, propionic acid, anhydrides of carboxylic acids, methanesulphonic acid, 4-toluenesulphonic acid and the like.

The conversion can be easily carried out in presence of water optionally containing an organic solvent. The reaction temperature can be kept at about -5 to 100°C.

The organic solvent can be selected from a group comprising of lower alkanols, ethers, esters, ketones, polar aprotic solvents, alkyl or cycloalkyl hydrocarbons or mixtures thereof. The lower alkanol is selected from methanol, ethanol, isopropanol, isobutanol, n-butanol and n-propanol. The ethers are selected from tetrahydrofuran, 1,4-dioxane, diethyl ether and diisopropyl ether. The esters are selected from ethyl formate, methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate, butyl acetate and amyl acetate. The ketones are selected from acetone, ethyl methyl ketone, methyl isobutyl ketone and diisobutyl ketone. Polar aprotic solvents are selected from N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone. Alkyl or cycloalkyl hydrocarbons can be selected from group comprising of cyclopentane, cyclohexane, cycloheptane, hexane, petroleum ether, heptane or mixtures thereof.

A twelfth aspect of the invention provides amorphous rosuvastatin calcium having an X-ray diffraction pattern as depicted in Figure I of the accompanied drawing.

A thirteenth aspect of the invention relates to pharmaceutical compositions and dosage forms comprising the amorphous rosuvastatin calcium prepared from crystalline rosuvastatin calcium to be used as HMG-CoA reductase inhibitor in treatment of hyperlipidemia.

A fourteenth aspect of the invention relates to a method inhibiting HMG-CoA enzyme in treatment of hyperlipidemia, comprising administering to a mammal in need thereof a therapeutically effective amount of the amorphous rosuvastatin calcium prepared from crystalline rosuvastatin calcium.

Figure I is X-ray powder diffraction (XRD) pattern of amorphous rosuvastatin calcium.
Figure II is X-ray powder diffraction (XRD) pattern of crystalline rosuvastatin calcium.
Figure III is X-ray powder diffraction (XRD) pattern of a mixture of largely amorphous mixed with some crystalline rosuvastatin calcium.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLE 1

Preparation of Amorphous rosuvastatin calcium from crystalline rosuvastatin calcium.

Step A) Preparation of crystalline rosuvastatin calcium

Amorphous rosuvastatin calcium (5.0 gm) was added to a mixture of water (50 ml) and acetonitrile (50 ml) at 15°C. The mixture was warmed to 40°C to obtain complete solution. The mixture was then cooled slowly to 25-30°C and stirred for 16 hours. The crystalline product was separated by filtration at ambient temperature and dried at 50°C under vacuum to give rosuvastatin calcium as white crystals.
Yield: 3.4 gm (68%) (XRD as per Figure II showed it to be crystalline material)

Step B) Conversion of crystalline to amorphous form

Crystalline rosuvastatin calcium (4.0 gm) was dissolved in tetrahydrofuran (12.0 ml) at about 25-30°C. The solution was filtered through celite bed and the bed was washed with tetrahydrofuran (2.0 ml). The clear filtrate and the washings were mixed and poured slowly in cyclohexane (120 ml) over 30 minutes at 25-30°C under vigorous stirring. The resulting mixture was stirred at 25-30°C for further 2.0 hours. The precipitated product was filtered and dried at 45°C under vacuum to give amorphous rosuvastatin calcium as white product.
Yield: 3.05 gm (76%) (XRD as per Figure I showed it to be an amorphous material)
HPLC Purity: 99.72%

EXAMPLE 2

Preparation of Amorphous rosuvastatin calcium from crystalline rosuvastatin calcium.

Crystalline rosuvastatin calcium (5.0 gm) was dissolved in tetrahydrofuran (15.0 ml) at about 25-30°C. The solution was filtered through celite bed and the bed was washed with tetrahydrofuran (2.0 ml). The clear filtrate and the washings were mixed and poured slowly in n-hexane (150 ml) over 30 minutes at 25-30°C under vigorous stirring. The resulting mixture was stirred at 25-30°C for further 3.0 hours. The precipitated product was filtered and dried at 45°C under vacuum to give amorphous rosuvastatin calcium as white product.
Yield: 3.6 gm (72%) (XRD as per Figure I showed it to be an amorphous material)

EXAMPLE 3

Preparation of Amorphous rosuvastatin calcium from crystalline rosuvastatin calcium.

Crystalline rosuvastatin calcium (5.0 gm) was dissolved in tetrahydrofuran (15.0 ml) at about 25-30°C. The solution was filtered through celite bed and the bed was washed with tetrahydrofuran (2.0 ml). The clear filtrate and the washings were mixed and poured slowly in heptane (120 ml) over 30 minutes at 25-30°C under vigorous stirring. The resulting mixture was stirred at 25-30°C for further 3.0 hours. The precipitated product was filtered and dried at 45°C under vacuum (about 5 to 10 mm of Hg) to give amorphous rosuvastatin calcium as white product.

Yield: 3.2 gm (64%) (XRD as per Figure I showed it to be an amorphous material)

EXAMPLE 4

Preparation of Amorphous rosuvastatin calcium from crystalline rosuvastatin calcium.

Crystalline rosuvastatin calcium (1.0 gm) was dissolved in tetrahydrofuran (3.0 ml) at about 25-30°C. The solution was filtered through celite bed and the bed was washed with tetrahydrofuran (0.5 ml). The clear filtrate and the washings were mixed and poured slowly in diethyl ether (25 ml) over 30 minutes at 20°C under vigorous stirring. The resulting mixture was stirred at 20°C for further 1.0 hours. The precipitated product was filtered and dried at 45°C under vacuum (about 5 to 10 mm of Hg) to give amorphous rosuvastatin calcium as white product.

Yield: 0.80 gm (80%) (XRD as per Figure I showed it to be an amorphous material)

HPLC Purity: 99.62%

EXAMPLE 5

Preparation of Amorphous rosuvastatin calcium from crystalline rosuvastatin calcium.

Crystalline rosuvastatin calcium (1.0 gm) was dissolved in tetrahydrofuran (3.0 ml) at about 25-30°C. The solution was filtered through celite bed and the bed was washed with tetrahydrofuran (0.5 ml). The clear filtrate and the washings were mixed and poured slowly in isopropyl alcohol (25 ml) over 30 minutes at 20°C under vigorous

stirring. The resulting mixture was stirred at 20°C for further 1.0 hours. The precipitated product was filtered and dried at 45°C under vacuum (about 5 to 10 mm of Hg) to give amorphous rosuvastatin calcium as white product.
Yield: 0.6 gm (60%) (XRD as per Figure I showed it to be an amorphous material)

EXAMPLE 6

Preparation of Amorphous rosuvastatin calcium from crystalline rosuvastatin calcium.

Crystalline rosuvastatin calcium (2.0 gm) was dissolved in tetrahydrofuran (6.0 ml) at about 25-30°C. The solution was filtered through celite bed and the bed was washed with tetrahydrofuran (0.5 ml). The clear filtrate and the washings were mixed and poured slowly in isopropyl acetate (60.0 ml) over 20 minutes at 25-30°C under vigorous stirring. The resulting mixture was stirred at 25-30°C for further 5 minutes. The precipitated product was filtered immediately and dried at 45°C under vacuum (about 5 to 10 mm of Hg) to give amorphous rosuvastatin calcium as white product.
Yield: 0.7 gm (35%) (XRD as per Figure I showed it to be an amorphous material)

EXAMPLE 7

Preparation of Amorphous rosuvastatin calcium from crystalline rosuvastatin calcium.

Crystalline rosuvastatin calcium (2.0 gm) was dissolved in dimethylsulphoxide (6.0 ml) at about 30-35°C. The solution was filtered through celite bed and the bed. The clear filtrate was poured slowly in water (15.0 ml) over 30 minutes at 25-30°C under vigorous stirring. The resulting mixture was stirred at 25-30°C for further 2.0 hours. The precipitated product was filtered and dried at 45°C under vacuum (about 5 to 10 mm of Hg) to give amorphous rosuvastatin calcium as white product.
Yield: 1.5 gm (75%) (XRD as per Figure I showed it to be an amorphous material)

EXAMPLE 8

Preparation of Amorphous rosuvastatin calcium from crystalline rosuvastatin calcium.

Crystalline rosuvastatin calcium (5.0 gm) was dissolved in tetrahydrofuran (25.0 ml) at about 25-30°C. The solution was filtered through celite bed and the bed was washed with tetrahydrofuran (2.0 ml). The clear solution was spray dried at 25-30°C, 600 Newtonlitre per hour nitrogen flow and at a rate of about 2.5 ml per minute. The material was recovered from receiver and dried at 40-45°C under vacuum (about 5 to 10 mm of Hg) for 6 hrs to get the tile compound.
Yield: 4.0 gm (80%) (XRD as per Figure I showed it to be an amorphous material)

EXAMPLE 9

Preparation of Amorphous rosuvastatin calcium from crystalline rosuvastatin calcium.

Crystalline rosuvastatin calcium (1.0 gm) was dissolved in tetrahydrofuran (6.0 ml) at about 25-30°C. The solution was filtered through celite bed and the bed was washed with tetrahydrofuran (0.5 ml). The clear solution was concentrated under vacuum at 45°C to get solids which were then dried at 40-45°C under vacuum (about 5 to 10 mm of Hg) for 6 hrs to get the tile compound.
Yield: 0.9 gm (90%) (XRD as per Figure I showed it to be an amorphous material)
HPLC Purity: 99.71%

EXAMPLE 10

Preparation of Amorphous rosuvastatin calcium from crystalline rosuvastatin calcium.

Crystalline rosuvastatin calcium (2.0 gm) was slurried in cyclohexane (10 ml) and the slurry was placed in a glass mortar. The slurry was triturated with pestle till the crystalline form was completely converted to amorphous form. The slurry was then filtered and the solid was dried under vacuum at 40-45°C to get amorphous rosuvastatin calcium.
Yield: 1.3 gm (65%) (XRD as per Figure I showed it to be an amorphous material)

EXAMPLE 11

Preparation of Amorphous rosuvastatin calcium from crystalline rosuvastatin calcium.

Crystalline rosuvastatin calcium (2.0 gm) was subjected to grinding using an agate pestle and mortar till it is completely converted to the amorphous form.
Yield: 1.70 gm (85%) (XRD as per Figure I showed it to be an amorphous material)

EXAMPLE 12

Preparation of Amorphous rosuvastatin calcium from crystalline rosuvastatin calcium.

Crystalline rosuvastatin calcium (1.0 gm) was dissolved in 1,4-dioxane (5.0 ml) at about 30-35°C. The clear solution was freeze-dried at a temperature of -20°C to get solids which were then dried at -20 to 10°C under vacuum (less than 0.1 mm of Hg) for 3 hrs to get the tile compound.
Yield: 0.98 gm (98%) (XRD as per Figure I showed it to be an amorphous material)

EXAMPLE 13

Preparation of Amorphous rosuvastatin calcium from rosuvastatin methyl ammonium salt.

Step A) Preparation of rosuvastatin lactone from rosuvastatin methyl ammonium salt.

Rosuvastatin methyl ammonium salt (20 gm) was added into mixture of ethyl acetate (100 ml) and water (200 ml) at 25-30°C and the pH of the reaction mass was adjusted to about 3.0 with 6N hydrochloric acid. The layers were separated and the organic layer is washed with water (50 ml). The organic layer was concentrated under vacuum to get an oily crude product which was mixed with toluene (50 ml). The reaction mass was refluxed for about 6 hours and the solvent was removed under vacuum at 60°C. The residue obtained was stirred with hexane (100 ml) and the separated solid was filtered. Dried the product under vacuum till constant weight at 40-45°C to get rosuvastatin lactone.

Step B) Conversion of rosuvastatin lactone to amorphous rosuvastatin calcium.

Rosuvastatin lactone as obtained in step A) was dissolved in methanol (100 ml) and water (100 ml). To this solution added, 8% sodium hydroxide solution till the pH of the reaction mass is about 8.5 to 8.7 and stirred for further 3 hours. After ensuring the absence of rosuvastatin lactone by TLC, solvent was removed under vacuum and the aqueous layer was washed with methyl tert-butyl ether (80 ml). The traces of methyl tert-butyl ether were removed under vacuum and to the aqueous layer added a solution of calcium chloride dihydrate (4.5 gm) in water (25 ml) at 20-22°C with vigorous stirring. After complete addition, mixture was stirred for further 2 hours at 20-22°C and filtered, washed the cake with water (20 ml) thrice and then dried at 45°C under vacuum to get amorphous rosuvastatin calcium.

Yield: 15.3 gm (83%) (XRD as per Figure I showed it to be an amorphous material)

EXAMPLE 14

Preparation of Amorphous rosuvastatin calcium from rosuvastatin lactone

Rosuvastatin lactone as obtained in step A) of Example 13 was dissolved in methanol (100 ml) and water (100 ml). To this solution added, 8% sodium hydroxide solution till the pH of the reaction mass is about 8.5 to 8.7 and stirred for further 3 hours. After ensuring the absence of rosuvastatin lactone by TLC, solvent was removed under vacuum and the aqueous layer was washed with methyl tert-butyl ether (80 ml). The traces of methyl tert-butyl ether were removed under vacuum and to the aqueous layer added a solution of calcium acetate (4.0 gm) in water (25 ml) at 20-22°C with vigorous stirring. After complete addition, mixture was stirred for further 2 hours at 20-22°C and filtered, washed the cake with water (20 ml) thrice and then dried at 45°C under vacuum to get amorphous rosuvastatin calcium.

Yield: 13.8 gm (75%) (XRD as per Figure I showed it to be an amorphous material)

EXAMPLE 15

Preparation of Amorphous rosuvastatin calcium from rosuvastatin methyl ammonium salt

Rosuvastatin methyl ammonium salt (10 gm) was added in water (50 ml) and added to it sodium hydroxide solution (8%, 9.0 ml) at 25-30°C and stirred for 20 minutes. The solution was filtered through celite bed and the bed was washed with water (20 ml). From the resulting clear filtrate, water was removed (about 40 ml) by vacuum distillation at about 60°C. To the resulting solution added water (40 ml) and a solution of calcium acetate (2 gm) in water (10 ml) at 20-22°C under vigorous stirring. Solid rosuvastatin calcium precipitates out from reaction mass. To the reaction mass added tetrahydrofuran (50 ml) and stirred for 10 minutes. Added sodium chloride (2.0 gm) to the reaction mass and stirred for further 10 minutes. Layers were separated and the organic layer was dried over powdered molecular sieves (10 gm). The molecular sieves were removed by filtration and the resultant solution was distilled azeotropically to remove water. After complete removal of water, tetrahydrofuran (50 ml) was added and the solution was filtered through celite bed. The clear filtrate was then concentrated under vacuum to get amorphous form of rosuvastatin calcium which was dried at 45°C under vacuum.

Yield: 7.6 gm (XRD as per Figure I showed it to be an amorphous material)

EXAMPLE 16

Preparation of amorphous rosuvastatin calcium from mixture of amorphous and crystalline rosuvastatin calcium

Step A) Preparation of mixture of amorphous and crystalline rosuvastatin calcium

Amorphous rosuvastatin calcium (6.0 gm) was dissolved in a mixture of tetrahydrofuran (18.0 ml) and water (2.0 ml) at 25-30°C. The resultant mass was stirred at 25-30°C for further 16 hours. To the mass added water (40 ml) and further stirred at 25-30°C for 1 hour. The separated solids were filtered and dried at 40-45°C under vacuum for 6 hrs.

Yield: 5.3 g (XRD of this material as per Figure III showed it to be a mixture of largely amorphous material mixed with some crystalline material)

Step B) Conversion of mixture of amorphous and crystalline rosuvastatin calcium to amorphous rosuvastatin calcium

The product obtained in Example 16 step A) (5.0 g) was dissolved in tetrahydrofuran (20 ml) and filtered to remove any undissolved particle. The clear solution was spray dried at 25-30^{0}C, 600 Newtonlitre per hour nitrogen flow and at a rate of about 1.5 ml per minute. The material was recovered from receiver and dried at 40-45 ^{0}C under vacuum to get amorphous rosuvastatin calcium.

Yield- 4.0 gm (80%) (XRD as per Figure I showed it to be an amorphous material)

HPLC Purity: 99.51%

EXAMPLE 17

Conversion of mixture of amorphous and crystalline rosuvastatin calcium to amorphous rosuvastatin calcium

The product obtained in Example 16 step A) (5.0 g) was dissolved in tetrahydrofuran (20 ml) and filtered to remove any undissolved particle. The clear solution was concentrated under vacuum at 45°C and the solid obtained was dried at 40-45 ^{0}C under vacuum to get amorphous rosuvastatin calcium.

Yield- 4.5 gm (90%) (XRD as per Figure I showed it to be an amorphous material)

EXAMPLE 18

Conversion of crystalline rosuvastatin calcium to amorphous rosuvastatin calcium

Crystalline rosuvastatin calcium (10.0 g) was added into mixture of ethyl acetate (100 ml) and water (100 ml) at room temperature. The pH of the resulting solution was adjusted 4.0 to 4.2 by adding dilute hydrochloric acid at 25°C. The layers were separated and organic layer was wash with water. The solvent was concentrated under vacuum to get oily residue.

The oily residue obtained above was dissolved in methanol (35 ml) and water (50 ml) at room temperature. The pH of the solution was adjusted with sodium hydroxide (8% solution in water) to about 8.5 to 9.0 and the resulting reaction mass was stirred for

further 1 hour at room temperature. Methanol was removed under vacuum. The oily residue was reconstituted in water (50 ml) and to the aqueous solution added a solution of calcium acetate (2.1 gm) in water (10 ml) at 20-22°C with vigorous stirring. After complete addition, mixture was stirred for further 2 hours at 20-22°C and filtered, washed the cake with water (20 ml) thrice and then dried at 45°C under vacuum to get amorphous rosuvastatin calcium.

Yield: 7.50 gm (75%) (XRD as per Figure I showed it to be an amorphous material)

HPLC Purity: 99.59%

Assay: 99.6% w/w

Dated this **17TH** day of **October, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

ABSTRACT

PROCESS FOR THE PREPARATION OF HMG-COA REDUCTASE INHIBITORS

The present invention relates to a process for the preparation of amorphous form of rosuvastatin calcium from crystalline rosuvastatin calcium, rosuvastatin methyl ammonium salt and rosuvastatin lactone.

Ranbaxy Laboratories Limited

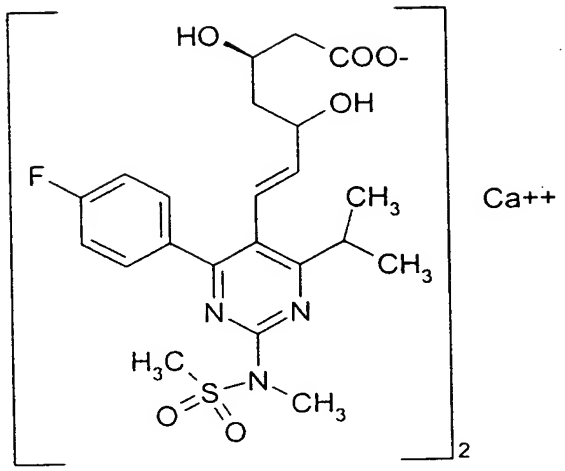
Application No.

No. of sheets = 06

Sheet 01 of 06

1704-DEL-03

22 OCT 2003



FORMULA I

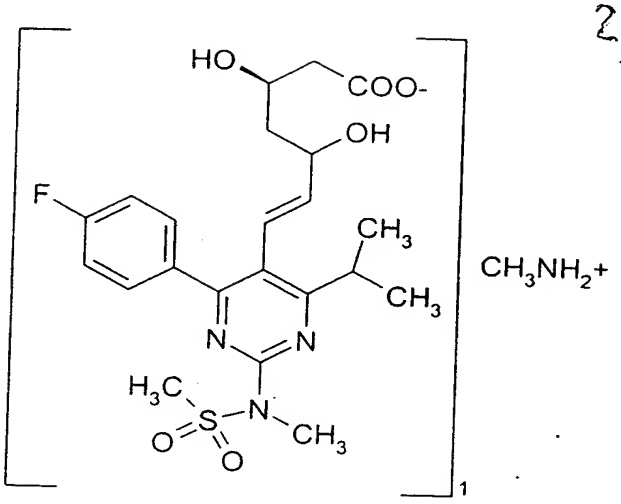
For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited
Application No.

1704 DEL 03

22 OCT 2003



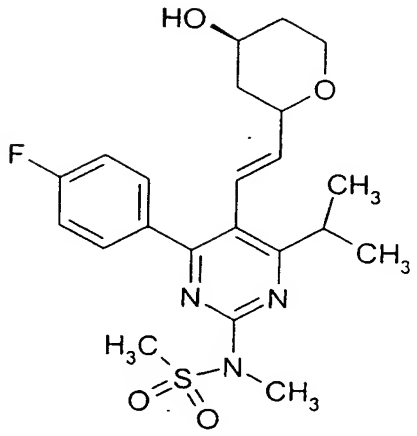
FORMULA II

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

1704 DEL 03

22 OCT 2003



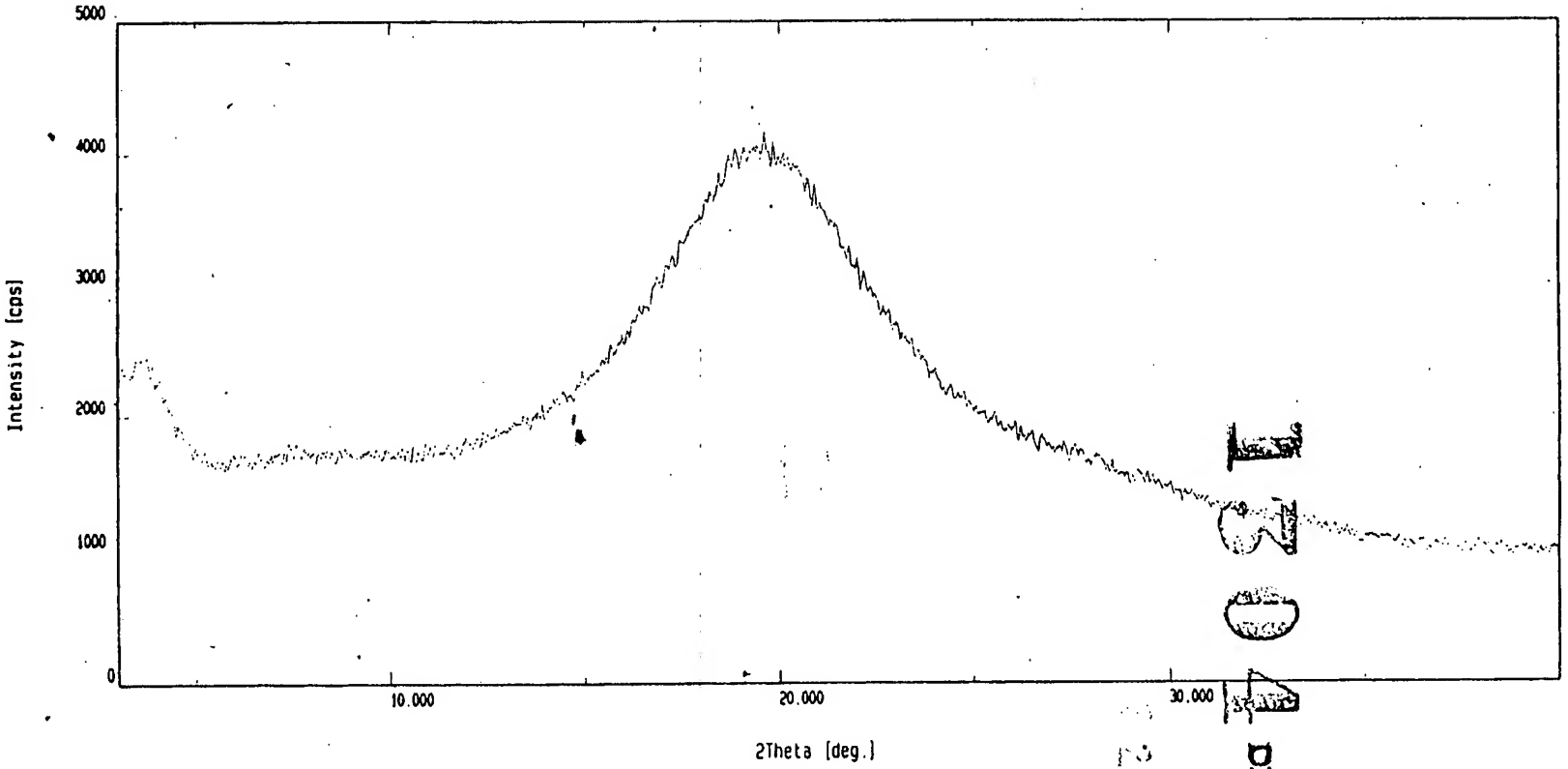
FORMULA III

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

ORIGINAL

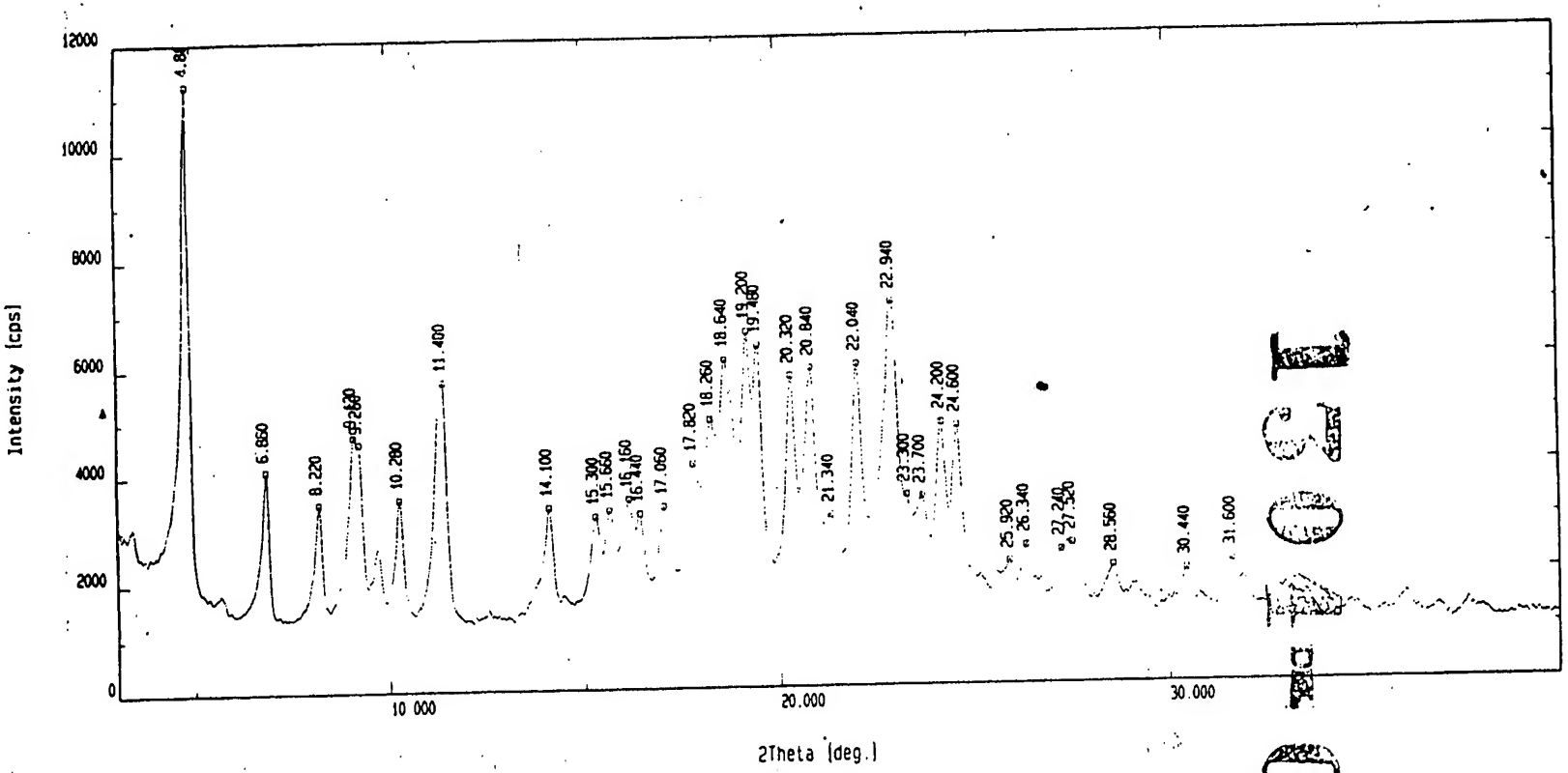
FIGURE 1



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

FIGURE II



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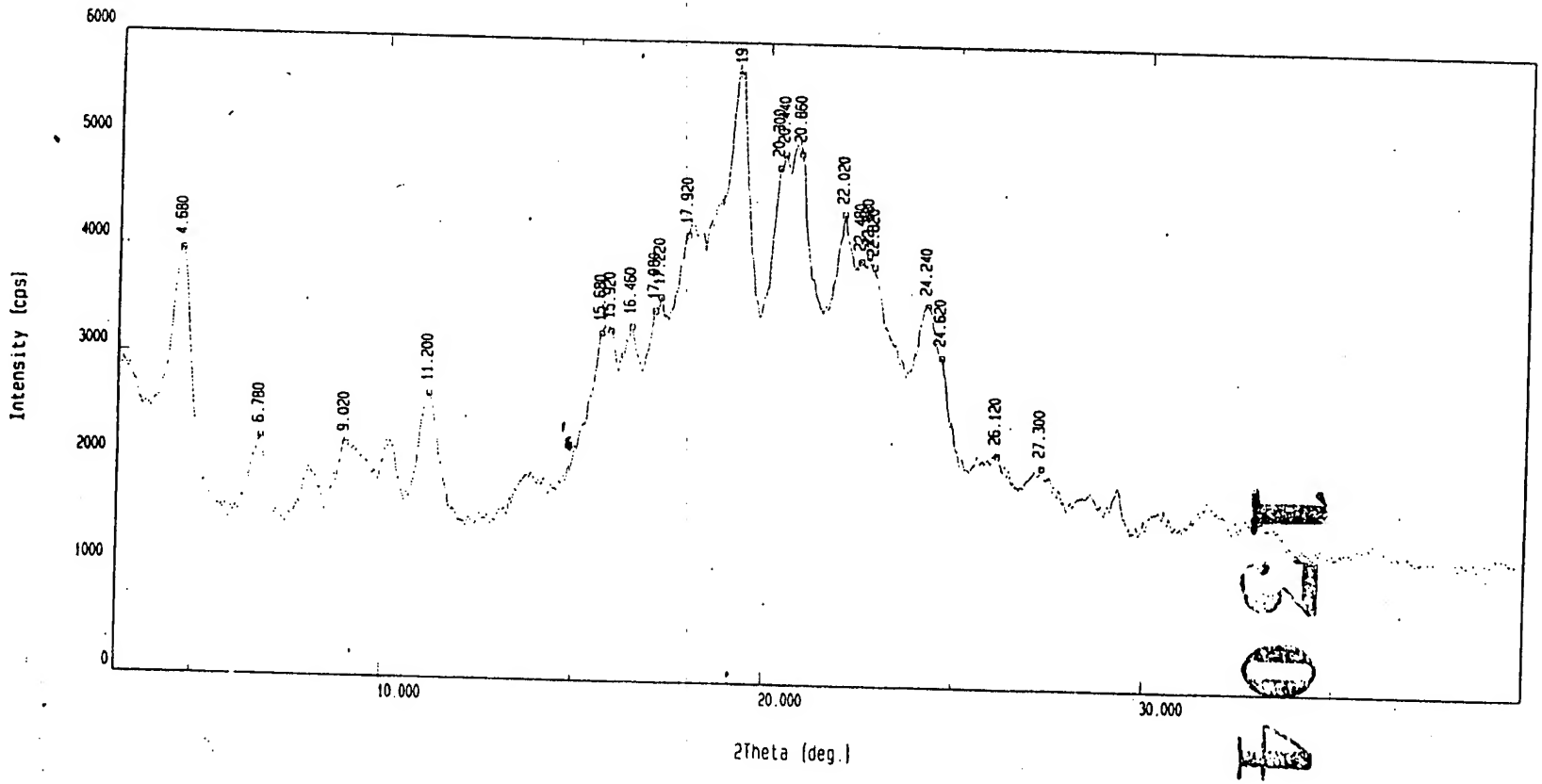
(Sushil Kumar Patawari)
Company Secretary

ORIGINAL

FIGURE III



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